Peroxisome proliferator-activated receptor γ2 Pro[12]Ala (rs1801282) polymorphism and breast cancer susceptibility: A meta-analysis

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Abstract. Several studies have investigated the correlation between the peroxisome proliferator-activated receptor γ2 (PPAR-γ2) Pro[12]Ala (rs1801282) polymorphism and the risk of breast cancer, with inconsistent results. For this reason, a meta-analysis was conducted to identify the potential correlation after pooling data from eligible case-control studies. Search strategies were conducted in PubMed, EMBASE and the COCHRANE Library in English and from VIP, CNKI and Sinomed in Chinese (all the papers were published before November 11, 2012) using appropriate terms. A total of 2,279 cases and 2,360 controls from four related case-control studies were included in this meta-analysis. According to the three eligible populations, the odds ratios (ORs) and 95% confidence intervals (CIs) on the risk of breast cancer for the CG versus CC and GG versus CC genotypes and the G versus C allele were 0.84 and 0.72-0.98, 0.92 and 0.32-2.61, and 0.98 and 0.84-1.13, respectively. The OR and 95% CI for CG+GG versus CC from the four study populations were 0.85 and 0.73-0.98, respectively. This meta-analysis supported the fact that the G allele of PPAR-γ2 Pro[12]Ala (rs1801282) modestly affects the risk of breast cancer. Nevertheless, further studies are required to enrich the evidence of this correlation.

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Introduction

Breast cancer is one of the most common types of cancer in females in developed and developing countries (1). The large number of novel breast cancer cases arising annually and the high mortality rate of breast cancer (2,3) encourage researchers to investigate the correlation between the potential environmental and genetic factors, and the risk of developing breast cancer. A number of genetic factors are assumed to correlate with the modification of the risk of breast cancer according to several of the most recently published studies (4-8). Adipose metabolism-related genetic variations may also modify the risk of breast cancer (9).

The peroxisome proliferator-activated receptors (PPARs) are a cluster of nuclear transcription factors, which are members of the nuclear hormone receptor super-family, and function in cellular differentiation and the regulation of carbohydrate and lipid metabolism (10). Polymorphisms in these receptors are assumed to affect the pathology of cancers and other diseases.

PPARs are classified into three predominant sub-types: PPAR-α, -β and -γ (11). PPAR-γ, also termed PPARG, is located on chromosome 3p25 in humans and dimerizes with the retinoid X receptor (RXR) to regulate target genes involved in adipocyte differentiation and insulin sensitization (12,13). PPAR-γ is also assumed to be correlated with malignant breast cancer epithelial cells (12). PPAR-γ2 is a sub-type of PPAR that is only expressed in adipose tissue (14). The Pro[12]Ala single nucleotide (rs1801282) polymorphism is a C/G mutation that may be associated with the modifications of the risk of a number of diseases (15-18).

Numerous studies have also been conducted to estimate the association between the Pro[12]Ala (rs1801282) polymorphism in the PPAR-γ2 gene and the risk of breast cancer, however the results have not always been consistent (19-22).

In the present study a meta-analysis on the eligible case-control studies was undertaken in order to analyze the

association between PPAR-γ2 Pro[12]Ala polymorphisms and breast cancer susceptibility.

Materials and methods

Search strategy. Multi-databases, including PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), EMBASE (http://www.embase.com/home) and the COCHRANE Library (http://www.thecochranelibrary.com/view/0/index.html) in English and VIP (http://lib.cqvip.com/), CNKI (http://www.cnki.net/) and Sinomed (http://www.sinomed.ac.cn/) in Chinese, were used to search the potential related published papers (all papers were published before November 11, 2012). The following keywords and subject terms were used: 'PPARγ2', 'PPARG' or 'proliferator-activated receptor gamma2' and 'breast cancer'. In addition, the search terms 'PPARG', 'breast cancer' and 'genetic association' were used in the HuGE Navigator. All the search terms were restricted to studies in humans. The references of the studies obtained were also searched in PubMed.

Inclusion criteria. Studies included in this meta-analysis were defined as: a) Case-control studies (including nested case-control studies; b) non-family based studies; and c) those evaluating the correlation between the PPAR-γ2 Pro[12]Ala (rs1801282) polymorphism and the risk of breast cancer.

Exclusion criteria. The articles that were case reports, system reviews, editorials, clinical guidelines and information articles for patients were all excluded. A study was also rejected if it did not provide information concerning PPAR-γ2 Pro[12]Ala polymorphisms.

Data extraction. Two investigators (QX Mao and HL Guo) searched and screened the potential associated articles for inclusion and appraisal. If there were any discrepancies, a discussion would be conducted in which other reviewers (LG Gao and HW Wang) would also be involved until an agreement was reached. The data abstracted from each publication consisted of first author, year of publication, country, ethnicity, study design, sample size, resources of controls and the PPAR-γ2 Pro[12]Ala polymorphism information. The study quality was quantified by the Newcastle-Ottawa-Scale (NOS) for case-control studies (23).

Statistical analysis. An unadjusted odds ratio (OR) and the corresponding 95% confidence interval (CI) of every eligible study was initially calculated. The Z-test was used to examine the pooled OR. The Q-statistic and I^2 statistical tests were used to measure the heterogeneity among the eligible studies. Fixed-effects models using Mantel-Haenszel methods and random-effects models were used in the meta-analysis. The Hardy-Weinberg (H-W) equilibrium was examined by a Pearson χ^2 test for the controls in every individual study. Potential publication bias was assessed by a Funnel plot and Egger's linear regression.

All analyses were performed by the Stata software, version 8.0 (Stata Corp LP, College Station, TX, USA). The tests were two-sided and $P<0.05$ was used to indicate a statistically significant difference.

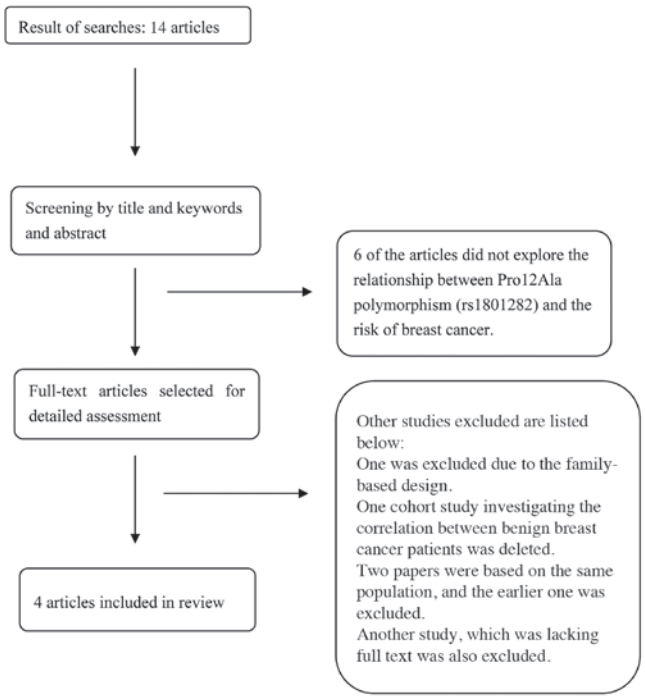

Figure 1. Identification process for eligible studies.

Results

Study characteristics and meta-analysis database. According to the search terms from the databases of the HuGE Navigator, PubMed, EMBASE and the COCHRANE Library when using the English language, fourteen potential correlated studies were collected. No correlated study published in Chinese was identified. Among these thirteen articles, one was excluded due to the family-based design (24). Six of the articles did not analyze the correlation between the Pro[12]Ala (rs1801282) polymorphism and the risk of breast cancer (9,11,25-28). One cohort study that investigated the correlation among benign breast cancer patients was also deleted (29). Two studies were based on the same population, and the former of them was excluded (30). Another study that lacked the full text was also excluded (31). Therefore, four individual studies remained for further analysis (19-22). A total of 2,279 cases and 2,360 controls available from the included reports for the PPAR-γ2 Pro[12]Ala polymorphism information were obtained. Breast cancer was confirmed by clinical examinations and from clinical records.

A dataset based on the extracted information from each included report was established (Table I). A quality assessment for the eligible studies according to the NOS is shown in Table II.

Quantitative synthesis. The average proportions of the frequencies of the G allele and the CG genotype from three eligible populations were 12.3 and 20.5%, respectively, in the patient cases and 13.7 and 23.2%, respectively, in the controls. The corresponding proportion of the CC genotype from four eligible populations was 80.5% in the patient cases and 78.1% in the controls. The genotype distributions of the G allele in the controls from every eligible study population satisfied the H-W equilibrium (all $P>0.05$).

Table I. Characteristics of studies included in this analysis.

ID	First author	Year	Country	Ethnicity	Source of controls	Genotyping method	Sample size case/control	Polymorphism distribution of PPARγ $Pro^{12}Ala$ case/control			Allele distribution of PPARγ $Pro^{12}Ala$ case/control	
								CC	CG	GG	C	G
1	Kim KZ	2012	Korea	Asian	PB	Sequence	400/452	366/406	33/40	-	-	
2	Petersen RK	2012	Denmark	Not mentioned	PB	TaqMan	798/798	616/569	167/209	15/20	182/229	197/240
3	Justenhoven C	2008	Germany	European	PB	TaqMan	593/622	452/462	135/145	6/15	1039/1069	147/175
4	Wang Y	2007	USA	Mixed	PB	TaqMan	488/488	376/375	87/98	15/5	839/848	117/108

ID, study id; PB, population-based.

Figure 2. Forest plots of odds ratio (OR) with 95% confidence interval (CI) of breast cancer associated with the PPAR-γ2 $Pro^{12}Ala$ polymorphism by fixed-effects model (CG vs. CC) heterogeneity, χ^2=2.12, P=0.347, I^2=5.5 %, Z=2.26 and P=0.024. The black square indicates the value of OR, and the size of the square is inversely proportional to its variance. The horizontal line represents the 95% CI of OR. The white diamond is the pooled results. The studies were ordered by the year published.

Figure 3. Forest plots of odds ratio (OR) with 95% confidence interval (CI) of breast cancer associated with the PPAR-γ2 $Pro^{12}Ala$ polymorphism by random-effects model (GG vs. CC) heterogeneity, χ^2=8.44, P=0.015, I^2=76.3%, Z=0.16 and P=0.874. The black square indicates the value of OR and the size of the square is inversely proportional to its variance. The horizontal line represents the 95% CI of OR. The white diamond is the pooled results. The studies were ordered by the year published.

Compared with the CC genotype, the CG genotype and CG+GG mixed genotypes carriers had a lower risk of breast cancer according to the three and four eligible populations, respectively. The ORs, CIs and heterogeneity values for CG and CG+GG on the risk of breast cancer were 0.84, 0.72-0.98 and 0.347 and 0.85, 0.73-0.98 and 0.441, respectively (see Fig. 2 and 4).

As the GG genotype did not modify the risk of breast cancer statistically (OR, 0.92; 95% CI, 0.32-2.61; heterogeneity, 0.015; Fig. 3) compared with the C allele carriers, those with the G allele did not have a statistically significant effect on the risk of breast cancer either. The corresponding OR, 95% CI and heterogeneity values were 0.98, 0.84-1.13 and 0.397, respectively (Fig. 5).

Publication bias. Funnel plots and Egger's tests were conducted to examine the publication bias (Fig. 6). No publication bias was identified (P=0.410).

Table II. Quality assessment for the eligible studies according to the NOS.

ID	First author	Selection, n stars	Comparability, n stars	Exposure, n stars
1	Kim KZ	4	2	1
2	Petersen RK	4	2	1
3	Justenhoven C	4	2	1
4	Wang Y	4	2	1

NOS for case-control studies: A study may be awarded a maximum of one star for each numbered item within the selection and outcome categories. Therefore, a maximum of four stars may be awarded for selection and three stars for outcome. A maximum of two stars may be awarded for comparability. More stars indicate a higher quality of the eligible studies. ID, study ID; NOS, Newcastle-Ottawa-Scale.

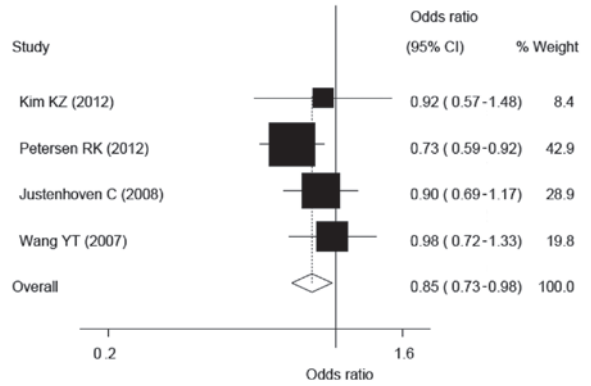

Figure 4. Forest plots of odds ratio (OR) with 95% confidence interval (CI) of breast cancer associated with the PPAR-γ2 Pro[12]Ala polymorphism by fixed-effects model (CG+GG vs. CC) heterogeneity, χ^2=2.69, P=0.441, I^2=0.0%, Z=2.30 and P=0.021. The black square indicates the value of OR and the size of the square is inversely proportional to its variance. The horizontal line represents the 95% CI of OR. The white diamond represents the pooled results. The studies were ordered by the year published.

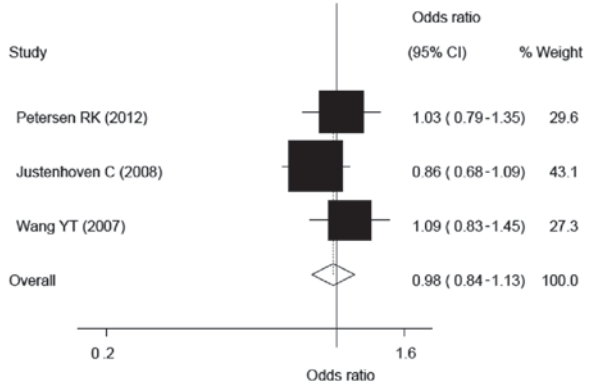

Figure 5. Forest plots of odds ratio (OR) with 95% confidence interval (CI) of breast cancer associated with the PPAR-γ2 Pro[12]Ala polymorphism by fixed-effects model (G vs. C) heterogeneity, χ^2=1.85, P=0.397, I^2=0.0%, Z=0.30 and P= 0.762. The black square indicates the value of OR and the size of the square is inversely proportional to its variance. The horizontal line represents the 95% CI of OR. The white diamond is the pooled results. The studies were ordered by the year published.

Discussion

A total of 2,279 cases and 2,360 controls from four eligible individual studies were included in the present study in order

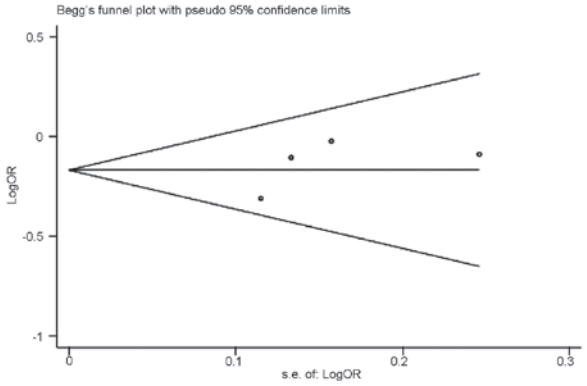

Figure 6. Begg's funnel plot of publication bias test Egger's test P=0.410. LogOR; natural logarithm of odds ratio. The horizontal line is the summary estimate, while the sloping lines are the expected 95% confidence interval (CI). s.e., standard error.

to investigate the association between the PPAR-γ2 Pro[12]Ala (rs1801282) polymorphism and the risk of breast cancer.

According to the results of the present study, the Pro[12]Ala polymorphism was demonstrated to be correlated with modifying the risk of breast cancer. The CG heterozygote and the CG+GG genotype carriers exhibited lower breast cancer incident risks in comparison with the GG genotype carriers. The corresponding ORs and 95% CIs were 0.84 and 0.72-0.98, respectively, for the CG carriers and 0.85 and 0.73-0.98, respectively, for the CG+GG carriers. Although, no statistical association between the Pro[12]Ala polymorphism and the breast cancer incident risk was demonstrated, when the comparisons were conducted between the GG and CC homozygotes or between the G and C alleles, there remained a potential effect from the GG homozygote or the G allele on the risk of breast cancer. The corresponding ORs and 95% CIs were 0.92 and 0.32-2.61, respectively, for the GG versus the CC homozygotes and 0.98 and 0.84-1.13, respectively, for the G versus C alleles.

The results of the present study were supported by certain previous studies. In a case-control study in Denmark conducted by Vogel *et al* (30), compared with the CC homozygote, the CG heterozygote and the CG+GG mixed genotype groups had a decreased risk of breast cancer. In addition, no statistically significant effect was observed from the GG homozygote on the breast cancer incident risk compared with the CC homozygote. Even in the multivariate adjusted model, such results did not change markedly. The corresponding multivariate-adjusted

ORs and 95% CIs were 0.66 and 0.45-0.96, respectively, for CG versus. CC, 0.67 and 0.46-0.97, respectively, for CG+GG versus CC and 0.81 and 0.29-2.29, respectively, for GG versus CC, respectively. The results of this study were also partially supported by German (19) and American (29) studies. In the German study (688 cases and 724 population-based controls), neither the CG heterozygote nor the GG homozygote modified the risk of breast cancer significantly. The corresponding ORs and 95% CIs were 0.96 and 0.74-1.27, respectively, for CG versus CC and 0.41 and 0.16-1.08, respectively, for GG versus CC (19). In the American study, a total of 994 post-menopausal females with benign breast disease were included in the cohort study, among which, 61 participants developed breast cancer after 14 years of follow-up. All the breast cancer patients were regarded as the cases and the others were analyzed as the controls. No statistically significant correlation was revealed between the $Pro^{12}Ala$ polymorphism and the breast cancer risk among the post-menopausal females with benign breast cancer. The corresponding ORs and 95% CIs were 0.53 and 0.24-1.19, respectively, for CG vs. CC, 0.79 and 0.10-6.03, respectively, for GG vs. CC and 0.55 and 0.26-1.19, respectively, for CG+GG vs. CC (29).

Contrary results were identified in the study conducted by Wang *et al* (20). In the nested case-control study, which included 488 cases and 488 controls, compared with the CC homozygote, the GG homozygote increased the risk of breast cancer (OR, 2.91; 95% CI, 1.05-8.04). At the same time, the CG heterozygote did not modify the risk of breast cancer significantly (OR, 0.88; 95% CI, 0.63-1.24).

The majority of the results, including the present meta-analysis, did not reveal that the GG homozygote modified the risk of breast cancer. However, the CG heterozygote and the CG+GG mixed genotype group modified the risk of breast cancer in certain studies (21). The majority of the results indicated the potential protective effect from the G allele on the risk of breast cancer. The lower frequency of the G allele in the study population included in the analyses may be a possible reason that a statistically significant correlation between the G allele/GG homozygote and the risk of breast cancer could not be demonstrated. Further studies based on a larger population are required to be undertaken in order to investigate such an association.

Several limitations of the present meta-analysis should be considered when interpreting the results. Due to the lower between-study heterogeneity and the limited number of studies involved in this meta-analysis, a sensitivity analysis was not conducted. In addition, a stratified analysis was not performed as the number of eligible published studies was insufficient for such a comprehensive analysis. Moreover, the language limitation may mean that information published in other languages may have been missed. Furthermore, no original data of the individual studies was obtained so only the summarized data about the potential confounding variables could be collected, and only unadjusted estimates were performed in the meta-analysis. However, the meta-analysis also had several advantages. All the cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Furthermore, the quality of the eligible studies included in the current meta-analysis was satisfactory, as they met the inclusion criterion and received a high quality score according to the NOS. All the study populations were also in H-W equilibrium.

In conclusion, this meta-analysis indicated that the G allele modestly modified the risk of breast cancer. However, due to insufficient comparative published studies involved, a systematic analysis of the correlation between the G allele and the risk of breast cancer could not be confirmed, but the study may have developed our understanding of the effect of the G allele on breast cancer. Further evidence from epidemiological studies is required in order to provide a clearer characterization of the involvement of the G allele and its genotypes in the genetic susceptibility to developing breast cancer.

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